REMARKS

Claims 245, 248-251, 253-255, 260, 264, 265, 268, 270, 272, 284, 288-290, 296, 299, 303, 304, 308-313 and 317 are currently being considered in the above-referenced application. As will be discussed in further detail below, claims 245, 265, 299, 308 and 324 have been amended to more distinctly claim that which Applicants regard as their invention. These amendments are supported by the specification. New claim 325 has been added to recite specific embodiments and are supported by the specification.

1. Sequence Compliance-Drawings

It is noted that the application fails to comply with the requirements of 37 CFR 1.821 through 1.825 since there are sequences in the drawings that do not contain a SEQ ID NO. In response, Applicants note that an amendment was submitted on November 12, 2004. This amendment contained an amendment of the "Brief Description of Figures" where sequences set forth in the figures are identified with SEQ ID NOS. A copy is attached hereto as Exhibit 1 for the Examiner's reference. Thus, compliance has been achieved.

2. The Rejections Over Bebenek

Claims 245, 248-251, 253-255, 260, and 264, are rejected under 35 U.S.C. 102(b) as being anticipated by Bebenek et al. (J. Biol. Chem. 1989.264(28) 16948-16956). The Office Action specifically states

> Applicant asserts that the mutations do not always occur in Bebenek and since the mutations do not occur 100% of the time, it would follow that a primary nucleic acid is sometimes obtained with the secondary nucleic acid or gene product. It is noted that the limitation "herein said primary nucleic acid is not obtained with said secondary nucleic acid or gene product" is not given much weight in light of the rejection under 35 U.S.C.112, 2"" paragraph explained below. The primary nucleic acid is not obtained with the secondary nucleic acid because the primary nucleic acid is the template.
>
> However, for arguments sake, there are certainly instances wherein the primary nucleic acid construct of

> Bebenek et al, (the HIV virion) gives rise to a secondary nucleic acid, which in turn gives rise to *a* sense nucleic acid which is the virus containing an average of five mutations and would therefore not be obtained with the primary nucleic acid construct. Furthermore, it is well accepted that HIV mutates from its original form.
>
> Applicant asserts that because the mutations do not always occur, the criteria for inherency has not been met and points to MPEP 2112. It is noted that MPEP 2113 states that the mere fact that a certain thing may result from a given *set* of circumstances is not sufficient. However, in the instant case Bebenek does not teach that mutations "may"occur. Bebenek et al, teaches that they *do* occur, at a rate of about 5 mutations per replication. While it may not be out of the realm of possibility to assert that HIV replication has occurred error-free at some point in time, this does not mitigate the fact that mutations have and do occur. Applicants have not provided any evidence or reasoning beyond mere assertion that refutes that Bebenek et a!. teaches that mutations occur during H1V replication, and that such mutations are inherent to the process of HIV replication. The rejection is maintained therefore.

Applicants respectfully traverse the rejection. The Office action states that "in the instant case Bebenek does not teach that mutations "may" occur. Bebenek teaches that they do occur". It appear that the phrase **primary nucleic acid is not obtained** with said secondary nucleic acid or said gene product" in the office Action has been interpreted to read that a product is obtained that is not the original (i.e. a positive recitation of production of a mutated product) whereas a proper reading of the claim is a requirement that there is no reproduction of the original product (i.e a negative recitation that stipulates the absence of "unmutated" product). Applicants, in order to more distinctly claim the subject matter of the invention recites that **said secondary nucleic acid or said gene product does not act as a template for the synthesis of said primary nucleic acid .** Thus, primary nucleic acid is not produced. As will be discussed in further detail below, amended claim 245 is supported by the specification on page 92.

Applicants note that reproduction of the original template can and will take place with a certain finite frequency in the experiments described by Bebenek et al. When the Bebenek paper says that there will be 5 mutations, this is in reference to an average or median value; in the population there will be some templates with 5 mutations and also some with 4 and some with 6 and continuing on in both directions. There will be a mathematically defined distribution such that instead of "while it may not be out of the realm of possibility" it is actually a statistical certainty that there will a discrete number of templates lacking any mutational changes thus violating the limitation as described above that requires that the secondary nucleic acid or gene product does not act as a template for a primary nucleic acid.

Furthermore, Applicants note that claim 245 specifically recites that secondary nucleic acid or the gene product does **not** act as a template for the synthesis of primary nucleic acid **when the construct is introduced into a eukaryotic cell**. In contrast, Bebenek et al. points out that the studies reported are a result of *in vitro* assays on an artificial template. The first sentence of the abstract states: "DNA-dependent DNA synthesis ***in vitro*** by human immunodeficiency virus-1 reverse transcriptase is relatively error prone." (emphasis added) . It is quite possible that the mutation rate is lower in vivo. This is acknowledged later in the abstract by the authors addition of a proviso: "a rate that, **if operative in vivo**, would produce 5 mutations per genome per round of replication" (emphasis added). Bebenek et al. are thus conceding that this extrapolation to an *in vivo* situation is based upon a tentative assumption since there are no experiments performed *in vivo* by this group. In a previous Office Action, the Examiner has stated that there is no support or rationale for why the rates would be different *in vivo* vs *in vitro*. However, data for *in vivo* situations is presented in the Bebenek et al. reference as part of the background for studies on human patients, where it is mentioned that the error frequency of HIV RT (the enzyme studied by Bebenek et al.) was estimated to be "10^{-3} nucleotide substitutions per site per year for the env gene". This correlates to an average of at least one mutation in a 1000 base segment per year or about 10 for a genome of around 10 kb (the approximate size of HIV). In short the *in vivo* patient results show about the same number of mutations after a year that Babenek et al. sees in a single

round of *in vitro* replication. This difference is explained at a later date when estimates for *In vivo* rates were finally carried out experimentally by other groups and the HIV mutation frequencies were reported to be $3x10^{-5}$ mutations per target base pair per cycle in Hela cells (Mansky and Temin 1994 J Virol 69; 5087-5094) (Exhibit 2). The title of this article is particularly telling: "Lower in vivo mutation rate of human immunodeficiency virus type 1 than predicted from the fidelity of purified reverse transcriptase". As stated in the abstract, the rate of mutations was observed to be 20 fold lower *in vivo* compared to *in vitro*, thereby providing objective proof of our previous contention. As such, even when there is a prediction of an average of 5 mutations per genome *in vitro*, this would translate to only a minority having even a single mutation *in vivo*.

Claims 246-251, 253-255, 250 and 264 ultimately depend from claim 245. Thus, arguments made with respect to claim 245 would apply to claims 246-251, 253-255, 250 and 264 as well.

In view of the above amendments and argumetns, Applicants assert that the rejections under 35 USC 102(b) over Bebenek et al. have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

2. The Rejections Under 35 USC §112

Two rejections under 35 USC 112 have been issued, one under 35 USC 112, second paragraph and another under 35 USC 112, first paragraph.

2.1 The Rejections Under 35 USC 112, Second Paragraph

Claims 245,248-251,253-255,260,264,265,308-311 and 324 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Several grounds are given and are discussed below:

2.1.1 Claim 265

It is asserted that the phrase "said antisense nucleic acid. sequence" lacks antecedent basis. Applicants traverse the rejection since, clearly "said antisense

nucleic acid sequence" refers to "an antisense nucleic acid sequence" recited a couple of words prior to 'said antisense nucleic acid sequence". However, in order to more distinctly claim the invention, claim 265 has been amended to recite (ii) an antisense nucleic acid sequence, said antisense nucleic acid sequence replacing sequences that participated in stem-loop formation in said snRNA.

2.1.2 Claims 308-311 and 324

It is asserted that there is insufficient antecedent basis for the limitation "said specific nucleic acid sequence" in claims 308 and 324. In response, claims 308 and 324 have been amended to recite "specific nucleic acid". Claims 309-311 depend from claim 308. Therefore, arguments made with respect to claim 308 would apply to these claims as well.

2.1.3 Claim 245

The Office Action specifically asserts

> Claim 245 recites, "wherein said primary nucleic acid *is* not obtained with said secondary nucleic acid or said gene product. It is not understood what is meant by "obtained with" in the context of the instant claim. The primary nucleic acid acts as a template for the synthesis of a secondary nucleic acid which acts as a template for the synthesis of a gene product, so it is not clear how the primary nucleic acid would be "obtained with the secondary nucleic acid or gene product" and the metes and bounds of the phrase "obtained with" are not understood. Claims 248-251, 253-255,260 and 264 are rejected because they depend from claim 245.

Applicants respectfully traverse the rejection. However, in order to more distinctly claim the subject matter of the invention, claim 245 has been amended to recite that the secondary nucleic acid product or "gene product" is unable to be used as a template to regenerate the primary nucleic acid. Applicants note that amended claim 245 is supported by the specification on page 92, lines 1-4 where it is stated

> **Propagation.** The generation or formation of a Production Center from a Primary Nucleic Acid Construct or the generation or formation of a Production center from

> another Production Center. However, production centers cannot produce a Primary Nucleic Acid Construct.

A "Production Center" is defined on page 91 as follows:

> As used herein the term production center is intended to cover secondary nucleic acid components which can be produced from a primary nucleic acid construct. Also covered are a tertiary nucleic acid component which could be produced form the secondary nucleic acid component, as well as any nucleic acid product which may be produced from the secondary nucleic acid component.

Claims 248-251, 253-255, 260 and 264 depend from claim 245. Thus, arguments made with respect to claim 245 would apply to these claims as well.

In view of the above arguments and amendments, Applicants assert that the rejections under 35 USC 112, second paragraph have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

2.2 New Matter Rejection

Claims 265, 268, 270, 272, 284, 288-290, and 296, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action specifically states

> Claim 265 recites, "wherein said antisense nucleic acid sequence replaces sequences that participated in stem-loop formation in said snRNA". Although Figure 41 depicts a U1 with antisense sequence inserted, there is not support for molecules having each of the characteristics of claim 265 and an antisense nucleic acid sequence that replaces sequences that participated in stem-loop formation in any snRNA, as instantly recited. Claims 268, 270, 272, 284 , 288-290, and 296 are rejected because they depend from claim 265.

Applicants respectfully traverse the rejection. In Applicants view, there is more than sufficient support for the phrase in question. With reference to claim 265, the Office Action acknowledges Figure 41 with an antisense insert but states that there is no support for the "replacement" language. This is exactly what Figure 41 displays. In the upper diagram the intact U1 is shown. The middle diagram shows

that Loop I as well as the A' region have been removed from stem-loop I and that Loop II as well as the B region of stem-loop II has also been removed. The lower diagram shows that the missing portion has been replaced with an anti-sense sequence. This removal and replacement is not just pictorially represented but also described in the text. In Example 26 on page 182, the bottom of the page states that Bcl I and Bsp E1 were used to remove a 49 base segment of the U1. The sequence of U1 is shown in Figure 43 thereby revealing the exact sites of the BclI and Bspe E1 restriction enzyme sites followed by the subsequent recombinant constructs where HIV antisense has replaced some of the U1 sequences as stipulated in the claim. Further support for claim 265 can be found in the paragraph bridging pages 163-164 where it is stated:

> .....Digestion of a clone of the human U1 operon with BCLI and BspEII (Figure 41) eliminates a sequence of 49 bases involved in the formation of the A and B loops formed by U1 RNA (Figure 41). Removal of this sequence thus both makes room for the addition of foreign sequence and eliminates binding of some snRNP proteins thus enabling the foreign sequence to be available for antisense inhibition free of potential steric hindrance by bound proteins. Elimination of the A and B loops would still allow formation of the C and D loops which are important for maintaining the re-importation signal (Figure 41)....

Applicants additionally note that claims 268, 270, 272, 284, 288-290, and 296 ultimately depend from claim 265. Thus, arguments made with respect to claim 265 apply to these dependent claims.

In view of the above arguments, Applicants assert that the rejection of claims 265, 268, 270, 272, 284, 288-290, and 296 under 35 USC 112, first paragraph has been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

3. The Rejections Under 35 USC 102(e)

Claims 299, 303,304,308,312 and 313 are rejected under 35 U.S.C. 102(e) as being anticipated by Calabretta et al. (US 5,734,039). The Office Action specifically states

> The invention of the above claims is directed to an isolated multi-cassette nucleic acid construct comprising either more than one promoter or more than one initiator or both more than one promoter and more than one initiator, which upon insertion into a eukaryotic cell produces more than one specific nucleic acid, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences.
>
> Calabretta et at. teach a composition for introducing two different antisense oligonucleotides specific for two different genes to a cell. Calabretta et al. teach a nucleic acid construct comprising a first promoter segment and a segment containing DNA of a cytoplasmic oncogene or proto-oncogene DNA, and a second promoter segment and a segment containing DNA of a nuclear oncogene or proto-oncogene. The DNA containing segments are in inverted orientation such that transcription of the DNA produces RNA complementary to the two mRNA transcripts of the two oncogene targets (see columns 8 and 9, for example). Calabretta et al. teach various modifications of the nucleic acids and teach means of delivery of the compositions.
>
> Therefore, the instant invention is anticipated by Calabretta et al.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claim 299 has been amended to recite that the multi-cassette nucleic acid construct comprises at least three promoters and/or at least three initiators and produces at least three specific nucleic acids from each of the promoters or initiators. As stated in the Office Action, the composition in Calabretta et al. introduces two different antisense oligonucleotides specific for two different genes to a cell. Therefore, claim 299 as amended does is not anticipated by Calabretta. Claims 303, 304, 308, 312 and 313 depend from claim 299. Thus arguments made with respect to claim 299 would apply to these claims as well.

In view of the above arguments and amendments, Applicants assert that the rejections under 35 USC 102(e) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

4. The Rejections Under 35 USC 103

Two rejections under 35 USC 103 have been issued. Both are discussed below:

4.1 Calabretta et al. in view of Binkley et al.

Claims 299, 309, 310 and 324 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al. (US 5,734,0391, in view of Binkley et al. (Nucleic Acids Research, 1995, Vol. *23,* No.16, pages 3198-3205). The Office Action specifically states:

> The invention of the above claims is directed to an isolated multi-cassette nucleic acid construct comprising either more than one promoter or more than one initiator or both more than one promoter and more than one initiator, which upon insertion into a eukaryotic cell produces more than one specific nucleic acid, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion *of* one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences. The specific nucleic acid binds to a specific cellular protein comprising a localizing protein or a decoy protein.....
>
> One would have been motivated to incorporate RNA oligonucleotides that bind to proteins instead of the antisense oligonucleotides in the system of Calabretta et al. because Binkley et al. teach that high affinity RNA ligands to proteins, such as NGF that localizes NGF-sensitive growing axons, can be. easily isolated using the SELEX procedure and teach that such RNAs may furnish useful diagnostic tools for the study of proteins. Since both types of nucleic acid oligonucleotides are used to determine binding interactions, as evidenced by the teachings of Calabretta et al., and Binkley et al., one would have been motivated to express the RNA ligands taught by Binkley et a!. in the system of Calabretta et al.
>
> One would have a reasonable expectation of success given that each of the nucleic acid molecules were known

> to bind with target molecules in a sequence specific manner, as evidenced by Calabretta et al. and Binkley et al. one would have a reasonable expectation of success *to* express the protein binding RNA molecules of Binkley et al. in the dual system of Calabretta et al., with the advantage of producing two different binding molecules at once.
>
> Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claim 299 has been amended to recite that the construct comprises at least three promoters and/or at least three initiators and produces at least three specific nucleic acids from each of the promoters or initiators. In Applicants view, it would not be obvious to combine Calabretta with Binkley et al. to obtain the construct of the present invention. Calabretta et al. teaches a composition for introducing two different antisense oligonucleotides specific for two different genes, specifically oncogenes to a cell. There is no suggestion regarding introducing three or more sequences. It would not occur to one of skill in the art to try to even obtain such a construct. Oncogenes have little variation in their sequences. Therefore, it would not occur to one of skill in the art that it may be useful to have a construct that produces three or more specific nucleic acids. Such constructs would be useful where the target sequences that interact with the specific nucleic acids on the construct have frequent mutational shifts such as in the case of HIV. Binkley merely teaches the existence of the RNA sequences that bind to various ligands. Even assuming arguendo that it would be obvious to combine Calabretta with Binkley to obtain a construct containing two specific nucleic acids, it would not be obvious to obtain a construct containing three or more specific nucleic acids given that there was no suggestion of such a construct in either of the cited references.

Claims 309, 310 and 324 depend from claim 299. Thus arguments made with respect to claim 299 would apply to these claims as well.

In view of the amendment of claim 299 and the above arguments, Applicants assert that the rejections of claims 299, 309, 310 and 324 under 35 USC 103 over Calabretta in view of Binkley have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

4.2 Calabretta in view of Binkley in view of Craig

Claims 299, 309-311and 324 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al. (US 5,734,039), in view of Binkley et al., (Nucleic Acids Research, 1995, Vol. 23, No.16, pages 3198-3205), as explained in the rejection under 35 U.S.C. 103(a) above, further in view of Craig et al. (WO 95108635). The Office Action specifically states

> The invention of the above claims is directed to an isolated multi-cassette nucleic acid construct comprising either more than one promoter or more than one initiator or both more than one promoter and more than one initiator, which upon insertion into a eukaryotic cell produces more than one specific nucleic acid, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein, wherein each specific nucleic acid binds to different target nucleic acid sequences. The specific nucleic acid binds to a specific cellular protein comprising a localizing protein or a decoy protein.
>
> Calabretta et. al. and Binkley *et* al. do not teach decoy proteins.
>
> Craig et al. teach the expression of viral decoy proteins under the control of a locus control region and teach that decoy proteins act as antagonists to natural proteins involved in the replication of the HIV virus. Craig et al. teach that a decoy protein can be used as a mutant of a transactivator protein that is capable of binding to the transactivator-responsive site on the host or viral genome, yet is incapable of activating transcription (see pages 2 and 3, for example).
>
> It would have been obvious to use the SELEX method to assay for RNA molecules that bind to a protein, as taught by Binkley et al. and to specifically use a decoy protein as the protein, as taught by Craig et al. One would have

> been motivated to screen for resultant RNA aptamers against a decoy protein because Binkley et at. teach that high affinity RNA ligands to proteins can be easily isolated using the SELEX procedure and teach that such RNAs may furnish useful diagnostic tools for the study of proteins. Since Craig et al. teach that decoy proteins are proteins that are useful to serve as a mutant that is capable of binding to a preferred site but yet is incapable of activating transcription, one would have been motivated to use the SELEX method of Binkley et al. to identify RNA ligands to any known protein, such as the decoy proteins of Craig et al.
>
> One would have a reasonable expectation of success given that Craig et al. teach the benefits of decoy proteins and Binkley et al. teach assaying for RNA aptamers to proteins and teach a method (SELEX) that is widely use to identify RNA molecules that bind to known proteins. Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, as noted above, claim 299 has been amended to recite that the construct comprises at least three promoters and/or at least three initiators and produces at least three specific nucleic acids from each of the promoters or initiators.

In Applicants view, it would not be obvious to combine Calabretta et al. with Binkley et al. and Craig et al. to obtain the construct of the present invention. As discussed above, Calabretta et al. teaches a composition for introducing two different antisense oligonucleotides. There is no suggestions regarding introducing three or more sequences. It would not occur to one of skill in the art to try to even obtain such a construct. Binkley merely teaches molecules that may bind to cellular protein. Craig et al. merely teaches expression of a viral decoy protein. In applicants view, it would not be obvious to combine all of these references. As noted above, combining Binkley with Calabretta would at best provide a construct that expresses two specific RNA sequences that binds to a cellular protein. Further, there was no suggestion regarding combining Craig with the other two. Craig et al. merely teaches the cloning of a protein and its therapeutic uses. There is no teaching regarding binding to a specific nucleic acid or facilitate transport.

In view of the amendment of claim 299 and the above arguments, Applicants assert that the rejections of claims 299, 309-311 and 324 under 35 USC 103 over Calabretta in view of Binkley have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

SUMMARY AND CONCLUSIONS

It is Applicants belief that the pending claims are in condition for allowance. However, if a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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Dated: 10/4/07

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